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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,835	03/08/2006	Takehisa Matsuda	2005_1807A	7978

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,835	MATSUDA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04-02-2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,30,32-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *1-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04-02-2009 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 1-26, 30, 32-37 and 39-40 are pending. Claims 30 and 37 have been amended by Applicants' amendment filed on 04-02-2009. Claims 1-26 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention. The election was made without traverse in Applicants' responses filed on in the replies filed on 11-05-2007 and 03-06-2008.
4. Accordingly, claims 30, 32-37 and 39-40 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103

To the extent that claims 30 and 40 read on epithelial cells of the oral mucosa, rejection of **claims 30 and 40** under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23):

6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A), and further in view of Medico et al., US Patent US 6551991 (Date of Patent, April 22, 2003) and Junqueira et al., (Basic Histology, 1986, Lange Medical Publications, pp. 64-65) has been withdrawn.

Though the combined references disclose mammalian host cells comprising AAV vectors encoding NK4, they fail to specifically teach transformant epithelial cell of the oral mucosa.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

Claims 30 and 37 have been amended to recite "a DNA encoding a protein having an amino acid sequence represented by SEQ ID NO:4" and "a peptide encoded by a DNA having a base sequence represented by SEQ ID NO: 2", respectively. To the extent that the phrase "represented by SEQ ID NO:4" is interpreted broadly to encompass proteins which have a structure "similar" to that of SEQ ID NO: 2 and thus embracing the full length of SEQ ID NO:4 or any portion, the following rejection applies.

Claims 30, 32-37 and 39-40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a method of inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis, which comprises administering to a mammal a cell-containing preparation comprising a cell which has a DNA as set forth in SEQ ID NO:2, which encodes a mature human

NK4 polypeptide a fibrous protein and a mesh sheet comprising a biodegradable resin to a mammal, the cell being an epithelial cell of the oral submucosa or a fibroblast,

does not reasonably provide enablement for other fragments or variants thereof which encode a protein which has an activity equivalent to NK4.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The specification provides insufficient data to enable claims directed to the fragments and/or variants of SEQ ID No. 2 based upon % homology. Thereby, specific issues including the functional limitations of DNA base sequences of any undetermined length with any degree of identity to the nucleotide sequence of SEQ ID NO. 2, that read on a genus of functional DNA able to exhibit an anti-tumor and an anti-angiogenesis activity, possibly because of by its

antagonism of the c-Met/HGF receptor, have to be examined and considered for patentability regarding the broadly claimed DNA base sequences.

The specification as filed discloses at page 30, the preparation and cloning into replication deficient Ad-NK4 expression vectors of the NK4 cDNA isolated from subcutaneous tissue Rats by using the primers identified as SEQ ID:5 and SEQ ID No. 6. Additionally, rat oral mucosal epithelial cells (OMEC) harvested and grown on a biodegradable collagen membrane were transfected with the Ad-NK4 (p. 33, lines 1-26). Cancerous mass were induced in mice and the effect of NK-4-sheets comprising the adenoviral-transduced OMEC was assessed in relation to growth and angiogenesis of s.c. tumors (Example 3). The specification is silent about cloning of any other fragments and/or variants with any degree of identity to the nucleotide sequence of SEQ ID No. 2. The specification does not provide any information on what amino acid residues are necessary and sufficient for the disclosed mature human NK4 polypeptide of SEQ ID NO: 4, such as properties of inhibiting angiogenesis, for example. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein (page 14, lines 23-25, bridging to page 15, lines 1-3). Since there were no other examples of functional marmoset HPRT proteins known that have the claimed structural homology with SEQ ID NO: 4 (for example), it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. The isolation of mRNA from subcutaneous tissue cells of rat (e.g., oral mucosal epithelial cells, OMEC) for preparation of cDNA using primers of SEQ ID Nos. 5 and 6 is of record. However, it

is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo et al, 1994). Rudinger (in Peptide Hormones, 1976) discloses that even for peptide hormones, which are much smaller than the instant NK4 protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see pages 3-4). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). Since it would require undue experimentation to identify other fragments and/or variants of the polypeptide of SEQ ID No. 4, it certainty would require undue experimentation to make and use the invention as claimed. Neither prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to make and use a genus of claimed fragments and/or variants of SEQ ID No. 2 encoding SEQ ID No. 4, i.e. the mature polypeptide NK4, wherein the coding sequence for amino acids 131-135 of the SEQ ID No. 3 are deleted, exhibiting the biological activity of a mature NK4, e.g., inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis in a mammal as broadly claimed.

As set forth in In re Fisher, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such

as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. In Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequence for each claimed SEQ ID NO, (e.g. SEQ ID NO: 4), and provides no guidance on determining which amino acid changes of the claimed nucleic acid of SEQ ID NO. 4 would have been functional to inhibit growth, invasion and metastasis of cancer or to inhibit angiogenesis.

Claim Rejections - 35 USC § 103

The instant claims are drawn to a method for inhibiting growth and metastasis of cancer cells in a mammal by administration of a cell-containing preparation comprising cells containing a DNA having a base sequence of SEQ ID NO: 2, which encodes a mature NK4 polypeptide fragment of HGF, a fibrous protein and a mesh sheet comprising a biodegradable resin, the cell being an epithelial cell of the oral submucosa or a fibroblast.

To the extent that claim 20 broadly reads on **"the cell being ... a fibroblast", the following rejections are maintained.**

Claims **30, 32, 34-37 and 39** remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) for the reasons already of record and the reasons set forth in the following paragraphs.

Folkman et al., teaches methods of gene therapy for treating cancer involving administration of DNA encoding kringle proteins that inhibits angiogenesis, metastasis and proliferation, particularly angiostatin (col. 4, lines 33-49; col.5, lines 5-12; col. 30, lines 20-23). Although Folkman focuses primarily on angiostatin, it teaches that kringle regions of other proteins, including hepatocyte growth factor (HGF) can be used (col. 6, lines 7-24, 28-30, and 57-59; col. 12, lines 60-65, col. 49, lines 15-35). Furthermore, in addition to *in vivo* gene therapy treaments, Folkman teaches *ex vivo* gene therapy treatment, wherein a cell is removed from the patient, transformed with a vector encoding the kringle protein, expanded, and then, the transformed cells is implanted back into the patient for expression of the gene product (col. 13, line 44; col. 14, lines 30-34). Folkman et al., teaches transformation of various cells including epidermal cells (col. 15, line 7) and treatment of accumulation of fibroblasts, i.e. fibroplasias (col. 6, line 16) (Current **claims 30, 34 and 37)**. Folkman et al., also teaches that cells are transfected with a recombinant DNA molecule comprising an angiostatin DNA sequence capable of expressing angiostatin(col. 17 lines 12-15) (Current **claim 35).** Additionally, Folkman et al.,

teaches combinations with therapeutic compositions such as collagen matrix (col. 21; lines 10-15, 20 and 28). (Current **claim 32)** and matrices made from biocompatible materials such polyglycolide (polymer of glycolic acid) (col. 11, line 53; col. 21, lines 26-36)(Current **claim 39).** In addition, Folkman et al., teaches viral vectors for use in gene therapy protocols including adeno-associated virus (col. 15, lines 30-31)(current **claim 36**).

Folkman et al., does not teach that NK4, containing four kringle domains, is a fragment of the larger HGF.

However, at the time the invention was made, Kuba et al., discloses that human NK4 containing four kringle domains and functions as an anti-tumor agent not only as an anti-angiogenesis factor abrogating angiogenesis induced by other angiogenic inhibitors, but also by its antagonism of the c-Met/HGF receptor as inhibitor of HGF. Thus NK4 antagonizes HGF-induced angiogenesis. Kuba et al., suggests that blockade of this receptor was responsible for the inhibition of metastasis by NK4 administration. Additionally, Nakamura exemplifies transformation of CHO cells which are fibroblasts with human HGF cDNA (EP, col. 12, lines 45-55, Example 1) (**Current claim 30**). Moreover, Nakamura, EP 1074264 (and WO 99/55361), discloses methods for inhibiting neovascularization using human NK4 polypeptides, exemplified by the amino acids of SEQ ID NO: 1 and 2. The EP document does not include the Sequence Listing; however, this EP application is the EP national phase application of WO 99/55361, which does include the Sequence Listing. The two polypeptides of Nakamura exemplified by SEQ ID NO: 1 and 2 are the same as instant SEQ ID NOs: 3 and 4, respectively, except that the Gln residue at position 1 is shown as PyrGlu (p. 7, paragraph [0025]). Nakamura discloses that cDNAs encoding the HGF polypeptides upon which the NK4 polypeptides are based were as

disclosed by Seki-A. (See entire document, especially cols. 3-4, 7-8, 12, and 13). Seki-A discloses cDNAs encoding two isoforms of human HGF (Fig. 2), a long isoform HGF/NK4, that corresponds to instant SEQ ID NO: 1, and a shorter isoform that corresponds to the instantly claimed SEQ ID NO: 2, HGF/NK4(del 5), wherein the nucleotide sequence encoding amino acids at positions 131-135 of the long NK4 polypeptide isoform is deleted (e.g., the nucleotide sequence at positions 483 to 497, and amino acids 162-166 in prepro-HGF or pre-NK4). The NK4 coding regions of the long and short cDNAs of Seki-A, i.e. nucleotides 94-1434 (long) and 94-482 plus 498-1434 (short), are identical to instant SEQ ID NOs: 1 and 2, respectively. Seki-A also taught that the sequence difference between the isoforms of human HGF did not appear to affect its HGF activity (pp. 323 and 326).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, to transform various cells with the cDNA encoding the human HGF/NK4(del 5) of Nakamura, (i.e. the polynucleotide sequence of SEQ ID NO: 2 encodes the NK4(del 5) polypeptide of SEQ ID NO: 4), to inhibit angiogenesis, metastasis and proliferation in the *ex vivo* therapy method of Folkman et al., particularly because, Kuba teaches that like angiostatin, NK4 is a polypeptide fragment of a larger HGF protein which contains four kringle domains and is a potent angiogenic inhibitors of tumors. Thus, it would have been obvious to one having ordinary skill in the art that substitution of the gene encoding angiostatin by the gene of SEQ ID NO: 2, encoding for the NK4 polypeptide of SEQ ID No. 4 comprising multiple kringle domains would have achieve the predictable result of inhibiting metastasis of cancer or angiogesis in an ex vivo method of treating cancer.

Response to Applicants' arguments as they apply to rejection of claims 30, 32, 34-37, 39 under 35 USC § 103

At page 8 of Applicants' remarks, Applicants essentially argue that (1) NK4 is structurally and patentably distinct from angiostatin as the amino acid sequence homology between the four kringle of NK4 and angiostatin reaches 47 %, and (2) that the present invention includes a biodegradable resin formed into a mesh sheet which is not taught by the combined references. Hence, Applicants allege that rejection of claims 30, 32, 34-37, 39 is unobvious from the cited references. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), as individual kringle domains of angiostatin have antiangiogenic activity and not necessarily the combined four kringle domains (p.6742, col. 1, lines 11-15), lower than 47% sequence homology between four kringle of NK4 and angiostatin may be sufficient for NK4 to reasonably have the claimed physiological properties. Conceivable, only one kringle domain of NK4 may be necessary for the claimed activity and the domain may have 100% homology to the corresponding kringle domain in angiostatin.

In turn, because NK4 has the proprieties predicted by the art, it further evidences that lower than 47% sequence homology is all what is required for NK4 to inhibit tumor growth and metastasis.

Regarding 2), Folkman et al., clearly teaches combinations of cell preparations comprising transformant cells with therapeutic compositions such as collagen matrix (col. 21; lines 10-15, 20 and 28) and matrices made from biocompatible materials such polyglycolide (polymer of glycolic acid)(col. 11, line 53; col. 21, lines 26-36), further evidenced by the claimed limitation of claim 39, thus making obvious the instant invention.

Claim 33 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., EP 1074264, Nakamura, T., WO 99/55361 and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32 and 34-37 and 39 above, and further in view of Allen et al., (US Patent 7,115,256; Date of Patent, Oct. 3, 2006).

The teachings of Folkman et al., Kuba et al. Nakamura, T. and Seki are outlined in the paragraph above. The combined references fail to teach that cells are deposited on the surface of the fibrous protein.

However, at the time the invention was made, Allen et al., discloses methods of treating psychiatric disorders by application to selected sites in the brain where healing is desired of genetically engineered cells coating the surface of a support matrix, said cells able to produce dopamine (col. 3, lines 10-15; col. 4, lines 10-13; col. 12, lines 55-60; col. 13, line 64; col. 14, lines 1-7). Additionally, Allen et al., discloses support matrices made of collagen (col. 12, line 39). Although Allen focuses primarily on therapeutic cells adhered to a support matrix which produce dopamine, it teaches that cells can be genetically modified to produce other genes of interest (col. 10, lines 55-67 bridging to col. 11 lines 1-20).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to modify the therapeutic compositions of Folkman et al., comprising transformed cells and a matrix of collagen, to deposit the transformed cells on the surface of a fibrous protein (e.g., matrix) as the scaffold to support cells as taught by Allen, particularly, because Allen successfully exemplifies modified cells adhered to support matrices of collagen able to express a

protein of interest at the desired site for therapeutic treatment. One of ordinary skill in the art, would have expected Applicant's invention to perform equally well with cell preparations transformed with other base sequences because the claimed transformed cell-containing preparations will have similar mechanical and biocompatibility properties. The references above provide all the elements of transformed cells with a DNA having a polynucleotide sequence of SEQ ID No. 2 encoding the amino acid of SEQ ID No. 4 deposited on the surface of the fibrous protein to obviate **claim 33.**

Note that Applicant has provided a single response that properly applies to the rejection of claims 30, 32, 34-37, 39 under 35 USC § 103 and claim 33 under 35 USC § 103, and is equally relevant.

Double Patenting

Claim 37 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 30 for the reasons already of record as set forth at pages 10-11 of the office action filed on 01-07-2009. Applicants have not submitted new arguments to rebut objection of claim 37 under 37 CFR 1.75

New Grounds of Rejection

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 32-37 and 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 30 is directed to a DNA having a base sequence represented by SEQ ID NO:2 or an amino acid sequence "represented by" SEQ ID NO: 4. It is unclear if the phrase "represented by" should be interpreted narrowly to encompass only materials that have a structure identical to the SEQ ID NO: or if the phrase should be interpreted broadly to encompass materials which have a structure "similar" to the SEQ ID NO:. The metes and bounds of the claims as whole are not clearly set forth.

Claims 32-37 and 39-40 are rejected insofar as they depend from claim 30

For the purpose of a compact prosecution the claims are interpreted as to a DNA having a base sequence of SEQ ID NO:2, and an amino acid sequence of SEQ ID NO: 4.

Claim Rejections - 35 USC § 103

To the extent that **claims 30 and 40** read **on epithelial cells of the oral mucosa,** the following rejection applies.

Claims 30 and 40 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman et al., US Patent 6,024,688 (Date of Patent Feb. 15, 2000) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T., (EP 1074264), Nakamura, T., (WO 99/55361) and Seki et al. (*Biochem. Biophys. Res. Commun.* 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32 and 34-37 and 39 above, and further in view of Medico et al., , US Patent US 6551991 (Date of Patent, April 22, 2003) and Mooney et al., (US Patent 5,885,829, Date of Patent March 23, 1999)

The teachings of Folkman et al., Kuba et al. Nakamura, T. and Seki are outlined in the paragraphs above. The combined references fail to teach that transformed epithelial cells of the oral mucosa.

However, at the time the invention was made, Medico et al., discloses transformation of a mammalian host cell with recombinant DNA obtained from structural domains derived from the N-terminal hairpin domain and four-kringle domains of HGF (col. 1, lines 49-54). In addition, Medico et al., teaches that target tissues of HGF are epithelial cells of different organs, such as liver, kidney, lung, breast, pancreas and stomach, and some cells of the hematopoietic and nervous systems (col. 2; lines 10-15). Though Medico et al., does not particularly disclose epithelial cells of the oral mucosa as mammalian host cell, at the time the invention was made, the state of the art teaches that it is well established the generation oral tissues from viable cells using *ex vivo* cell culture as evidenced by Mooney et al., Additionally, Mooney et al., discloses viable oral tissue cells genetically engineered with a recombinant vector to express a gene of interest (col. 9, lines 5-10).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, to transform various cells with the cDNA encoding the human HGF/NK4(del 5) of Nakamura, (i.e. the polynucleotide sequence of SEQ ID NO: 2 encodes the NK4(del 5) polypeptide of SEQ ID NO: 4), to inhibit angiogenesis, metastasis and proliferation in the *ex vivo* therapy method of Folkman et al., particularly because, Kuba teaches that like angiostatin, NK4 is a fragment of a larger HGF protein containing four kringle domains which is a potent angiogenic inhibitors of tumors. Thus, it would have been obvious to one having ordinary skill in the art that substitution of the gene encoding angiostatin by the gene of SEQ ID

NO: 2 encoding for the NK4 polypeptide of SEQ ID No. 4 comprising four kringle domains would have achieve the predictable result of inhibiting metastasis of cancer or angiogesis in an ex vivo method of treating cancer. Furthermore, it would have been *prima facie* obvious for one of ordinary skill in the art, on the combined teachings of Medico et al., and Mooney to make and use a cell-containing preparation comprising known cell lines able to be transformed with a recombinant vector including epithelial cells of the oral mucosa, particularly, because Mooney successfully exemplifies that in *vitro* transformant cells from oral tissue of an animal are well known in the art. Thus, it would have been obvious for the skilled artisan to transform epithelial cells of the oral mucosa with a recombinant vector to achieve the predictable result of expressing an amino acid sequence of SEQ ID NO. 4 to target cancer tissue and to inhibit angiogenesis. The references above provide all the elements of epithelial cells of the oral mucosa transformed with a rAAV to anticipate claims 30 and 40.

Conclusion

Claims 30, 32-37 and 39-40 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633